FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Oncologic Drugs Advisory Committee

QUESTIONS

March 22, 2010

NDA 022-481
PIXUVRI (pixantrone dimaleate) injection

APPLICANT: Cell Therapeutics, Inc.

PROPOSED INDICATION: as a single agent treatment for patients with recurring or refractory (difficult to treat), aggressive non-Hodgkin's lymphoma (NHL) who have received two or more prior lines of therapy

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Trial Background

This application is based on a single incomplete trial of single-agent pixantrone for the treatment of patients with relapsed or refractory aggressive non-Hodgkin's lymphoma who have received two or more prior lines of therapy. Pixantrone is an aza-anthracenedione. Patients were required to have demonstrated prior response to anthracyclines/anthracenediones, to have an EF $\geq$ 50%, and to have received < 450 mg/M^2 of doxorubicin or its equivalent. Patients were randomized to pixantrone or a choice of 8 comparator therapies. The primary endpoint was complete response and complete response unconfirmed (CR/CRu) by independent review. Patients were also followed for PFS and OS.

The study was stopped early, after completion of only 44% of planned enrollment, due to poor accrual. The timing of this study stop was not pre-specified in the original statistical analysis plan. Poor accrual occurred worldwide, but was most evident in the United States, where only 8 patients were enrolled, despite the opening of 28 US sites. The applicant considered this poor accrual to be related to a number of factors, including a preference for combination regimens in the US and Western Europe, a preference for palliative care in late-stage disease, the wide-spread adoption of front-line rituximab during the course of the study, and the limited availability of a patient population meeting their eligibility criteria.

Trial Results

The primary analysis was a comparison of CR/CRu in the intent to treat population. Twenty percent (14/70) of patients in the pixantrone arm and 5.7% (4/70) of patients in the comparator arm achieved CR/CRu. However, 5/14 patients with CR/CRu in the pixantrone arm had ineligible, generally low-grade, disease by retrospective central histologic review, resulting in a CR/CRu rate of 9/54 (16.7%) on the pixantrone arm and 3/50 (6.0%) on the comparator arm. FDA-initiated radiologic review of all panel-assessed CR/CRus determined that four of the patients on the pixantrone arm and one on the comparator arm had responses that did not qualify as CR/CRu.

The p-value for the comparison of CR/CRu was 0.021. However, the required p-value with 44% of patients accrued was 0.0096. Based on statistical methods that would have been appropriate for an interim analysis at 140 patients, the primary endpoint (CR/CRu) did not achieve the required level of statistical significance, leaving no alpha for evaluation of secondary endpoints and rendering all such additional analyses exploratory.

Major safety concerns included adverse events leading to death (17.6% of patients in the pixantrone arm and 7.5% of patients in the comparator arm) and adverse events leading to discontinuation (36.8% of patients in the pixantrone arm and 31.3% of patients in the comparator arm). Common adverse

events (≥ 20.0%) included neutropenia, anemia, leukopenia, thrombocytopenia, pyrexia, asthenia, cough, and ejection fraction decreased. On the pixantrone arm, 7.4% of patients experienced grade 3-4 febrile neutropenia compared to 3.9% of patients in the comparator arm. In addition, 25.0% of patients on the pixantrone arm (4.4% grade 3-4) and 11.9% of patients on the comparator arm (1.5% grade 3-4) developed cardiac dysfunction.

Major Concerns

Our main concerns regarding this application are:

1) Whether the application provides substantial evidence of efficacy;
2) Whether these results are generalizable to the US population; and
3) Safety of pixantrone in light of increased rates of cardiotoxicity and febrile neutropenia on the pixantrone-treated arm.

Substantial Evidence of Efficacy

A higher level of evidence of efficacy is required whenever a single, randomized trial is used to support an NDA. When a single, incomplete trial is used to support an application for a new molecular entity with no prior approval history, this evidence should be especially persuasive. The p-value for the comparison of CR/CRu was 0.021. However, the required p-value with 44% of patients accrued was 0.0096.

The results are not clearly generalizable to the US population, as only 8 US patients were enrolled. The prior treatment characteristics of these 8 US patients were different from those of the population as a whole, and none achieved complete response or unconfirmed complete response.

Safety Concern

Patients treated with pixantrone experienced increased rates of febrile neutropenia and cardiotoxicity. The rates of febrile neutropenia and neutropenia leading to discontinuation were approximately double those of the comparator arm.

Question to ODAC (VOTE):

- For a single randomized trial to support an application for drug approval, it should be well-executed, internally consistent, and include statistically persuasive efficacy findings.
- Phase 3 trial stopped at 44% of planned enrollment due to poor accrual, with only 8 US patients enrolled at 28 US sites.
- The CR/CRu rate was 20.0% (14/70) on the pixantrone arm vs. 5.7% (4/70) on the comparator arm. This difference was not statistically significant. If only patients with centrally confirmed aggressive histology are included, the CR/CRu rate becomes 16.7% (9/54) vs. 6.0% (3/50).
- Secondary endpoints, including progression-free survival and overall survival, cannot be adequately evaluated in this incomplete trial.
- Adverse events of concern include cardiac dysfunction and febrile neutropenia. The most common grade 3-4 adverse events (≥10%) were neutropenia, leukopenia, thrombocytopenia, and anemia.

Does this single incomplete trial meet the criteria necessary for a single randomized trial to support approval?